Follicular lymphoma

M. Ghielmini*

Medicine, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Follicular lymphoma is an indolent and usually incurable disease. It has been therefore traditionally approached either by watch and wait or with single-agent treatments. The purpose was to maintain a good quality of life for a prolonged time. More aggressive regimens, including polychemotherapy, high-dose chemotherapy with stem-cell rescue and the emergence of new cytotoxic drugs have significantly improved the remission duration but could never demonstrate an impact on overall survival. In the past decade, through the addition of drugs acting on the immune system such as interferon or rituximab, the survival of follicular lymphoma patients could be improved by the range of several years. As a consequence several clinicians believe that we are near to a cure for follicular lymphoma so that the first-line treatment should be more aggressive to reach this goal. Nevertheless, at present, none of the new strategies can be shown to cure. We believe that even in the presence of many possible treatment options, watch and wait remains a good option for many patients with follicular lymphoma. When treatment is needed, chemotherapy with rituximab is the standard even though none of the chemotherapy regimens can be shown to be superior. As quality of life remains an issue, the combination of rituximab and bendamustine, a drug with high efficacy and a favourable toxicity profile, is a good new option for patients.

Key words: bendamustine, CHOP, follicular, lymphoma, rituximab, transplantation, watch and wait

introduction

Follicular lymphoma is an easy-to-diagnose indolent and incurable disease. Histologically, it is composed mainly of centrocytes with a variable component of centroblasts, the frequency of which gives the grade (1, 2 or 3, depending on the percentage of centroblasts). It is the most frequent lymphoma in the western world after diffuse large B-cell lymphoma and it is by far the most frequent indolent lymphoma [1], being therefore often used as model on which to build the treatment for all other indolent lymphomas. Its median survival was for decades evaluated to be ~9–10 years, but with the advent of new treatment modalities and better supportive care it has increased to ~14 years [2, 3]. The survival curve of these patients is characterized by a continuously descending straight line never reaching a plateau. The prognosis is determined by several clinical and biological factors, the most commonly used being the follicular lymphoma international prognostic index (FLIPI) [4]. Despite the introduction of new anti-lymphoma agents from the 1960s to the 1990s, the survival curves of these patients seemed not to move or to move only a little. It is only in the past decade that, thanks to the introduction, first, of interferon [5] and later, of rituximab and radio-immunotherapy (either alone or in combination with chemotherapy) that the median survival of this patient population has significantly increased [6]. Because rituximab shows a better therapeutic index compared with interferon, it has been substituted for the latter and become the standard treatment of indolent lymphomas, used either alone or in combination with chemotherapy. A number of questions remain open in the management of follicular lymphoma. In this update we will address only three of them:

(i) is watch and wait still an option?
(ii) what is the standard first-line treatment?
(iii) is there still a role for auto/allo-transplantation?

is watch and wait still an option?

The history of a patient with follicular lymphoma is one of many treatment lines alternated by treatment-free intervals that can last from months to many years. Each treatment that usually reaches a remission (partial or complete), is followed by a period of watch and wait and subsequent treatment when the disease again becomes symptomatic or starts growing rapidly. As this process goes on for many years, ending with the death of the patient either because of or with the disease, the question has always been open as to whether first-line treatment should be administered at diagnosis or only in the case of clinical need. Theoretically, waiting to treat could cause irreversible organ damage (if the disease is left to grow until an organ such as the kidney, the liver or the spinal cord is compressed), reduction of the patient’s performance status or increased resistance to next chemotherapy and, most feared of all, risk of transformation to high-grade lymphoma. While a reduction in the patient’s fitness can be avoided by careful and
regular examination of the patient, allowing for immediate treatment in the case of deterioration, the risk of the appearance of resistant clones or worse, transformation to high-grade disease, could be more of a concern. Nevertheless, studies comparing the response rate at diagnosis or after a period of watch and wait have not shown a difference in response rate, and several series observing the incidence of transformation could show that this is the same for patients treated with chemos- or radiotherapy at diagnosis and patients observed until treatment was clinically needed [7]. The main argument in favour of watch and wait is that four randomized trials carried out in the last decades could not show any advantage in survival of the immediate treatment approach [8]. On the contrary there are potential advantages of waiting, which are a delay in the acute and, most important, in the appearance of delayed side-effects of chemotherapy and that infertility or early menopause for patients of young age is avoided or massively delayed. Even though in the observation studies the median time to the start of treatment was in the region of 3 years, a quarter of the patients could wait up to 10 years before starting treatment, which translates to a substantial improvement in delayed side-effects and improved quality of life for this relevant proportion of patients.

**which is the standard in first-line treatment?**

Many treatments were used in first line for follicular lymphoma, none of which could be shown to be better than another. Historically, single-agent treatments such as chlorambucil or cyclophosphamide were used, and in the following decades they were combined with prednisolone, vincristine and subsequently also doxorubicin in aggressive lymphomas. Other combinations have included purine analogues, interferon or even more aggressive combinations as in diffuse large B-cell lymphoma. The experience of these decades showed that the more aggressive the regimen, the longer the disease-free survival. Nevertheless, this prolongation of disease-free survival could never be shown to significantly translate into improved overall survival [9]. The number of patients still in remission after first-line treatment is in the region of 30% at 5 years and 20% at 7 years, independently of the intensiveness of the regimen and is probably rather dependent on patient characteristics. Recently, a new alkylating agent comprising a purine analogue moiety in the molecule (bendamustine) proved to be at least equivalent to CHOP when combined with rituximab and administered to patients with indolent lymphomas [10]. Because bendamustine has substantially fewer side-effects than CHOP, the combination of bendamustine and rituximab constitutes today a very good option for patients with follicular lymphoma. A number of studies are still ongoing in Europe and the USA, comparing different regimens with CHOP and rituximab in order to determine which is the one with the best therapeutic index.

**is there still a role for auto/allo-transplantation?**

High-dose chemotherapy or total body irradiation followed by rescue with autologous bone marrow or peripheral stem cells is frequently used to rescue patients in first or second relapse and, in this setting, could be shown (although with very weak evidence) to improve survival in relapsed follicular lymphoma patients [11]. It was therefore logical to try this strategy also in first-line treatment. Unfortunately, three randomized studies carried out with classical chemotherapy induction and one study carried out with the addition of rituximab both to the induction and to the high-dose therapy, could demonstrate an improvement in progression-free but not in overall survival [12]. The major explanation for this was the important incidence of secondary leukaemia and myelodysplastic syndromes. Because many of the patients experience long first and second remissions, it is today suggested that the high-dose chemotherapy strategy should be reserved for patients with early or aggressive relapse, who are young and fit enough to tolerate the procedure.

Allogeneic transplantation associates the debulking effect of high-dose chemotherapy with the immunological graft versus lymphoma effect. It is therefore capable of achieving a plateau in the survival curve and is indeed probably the only treatment modality with a chance of cure [13]. Unfortunately, this modality, despite the better results with a reduced-intensity conditioning method, is still linked to a high early mortality rate, so that it is recommended for allo-transplant patients only if they present with very chemo-resistant disease, are fit enough and dispose of a compatible donor.

**conclusions**

In front of a new patient with follicular lymphoma, one should first evaluate the prognosis, the symptoms and the patient’s priority [14]. Prognosis is best evaluated by determining stage, FLIPI prognostic factor and histological grade. Symptoms can be absent or mild or else life- or organ-threatening. The patient’s priority may not be set upon prolonging survival but, especially for elderly patients, could be mainly in the direction of better quality of life. Taking into consideration all these data the doctor can orient the patient rather towards a watch and wait strategy, a more intensive treatment of multi-agent chemotherapy combined with rituximab followed by rituximab maintenance or a ‘soft’ or ‘patient-friendly’ treatment including single-agent rituximab, chlorambucile, cyclophosphamide, fludarabine or bendamustine (all of these eventually combined with rituximab) all possibly followed by zevalin consolidation [15].

We conclude that watch and wait remains an option, that R-CHOP is not the standard first-line treatment and that transplantation should be kept for cases of (aggressive) relapse.

**disclosures**

The author declares no conflict of interest.

**references**


